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Occult Hepatitis B among Patients under Hemodialysis at Mansoura University Hospitals: Prevalence and Risk Factors

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Abstract:

Background: In spite of the progress made in the prevention of transfusion transmitted infections over the last decade, transmission of hepatitis viruses like B and C infection through transfusion of serologically negative blood has been documented among susceptible patients who are under hemodialysis due to end stage renal failure.

Aim: The present study was performed to diagnose Occult Hepatitis B among patients under hemodialysis at Mansoura University Hospitals and to determine the risk factors for such infection.

Material and method: The study was conducted on 96 patients attending Mansoura University hospitals for hemodialysis with age range from 26 to 65 years. In addition, one hundred sixty seven healthy blood donors were included in the study and considered as a control group. Blood samples were obtained from each subject and subjected to full biochemical analysis for liver function tests and serological markers for hepatitis C IgG (HCV IgG), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody(HBs Ab), hepatitis B core IgG and IgM (HBc IgG & HBc IgM). Furthermore molecular study for hepatitis B viral DNA and its genotypes were performed by multiplex polymerase chain reaction.

Results: HBV DNA was detected in 18(18.8%) compared to blood donors (2.4%) with statistically significant difference (P=0.0001). Hepatitis core IgG was positive in 19 patients (19.8%) compared to control group (2.4%). The majority of patients under hemodialysis had positive HBV DNA in absence of any serological markers (72.2%). The genotypes of hepatitis B virus in patients under hemodialysis were mainly C (44.4%), followed by A (27.8%) then B (22.2%), while in healthy control only two genotypes were detected C (50%) and mixed type D&F type (50%) with statistically significant difference between patients and control subjects (P=0,0001). Risk factors analysis for occult hepatitis B in patients under hemodialysis revealed significant association between duration of hemodialysis (P=0, 0001-95%CI 1.01-1.05) and the numbers of transfused blood units (P=.0001 95%CI 1.1-1.5).

Conclusion: From this study we can conclude that occult hepatitis B is mundane among hemodialysis patients. The prolonged duration of dialysis and the number of blood units are major risk factors for acquiring such infection.

Keywords: Hemodialysis; Occult hepatitis B virus; Seronegative

Introduction

Hepatitis B virus (HBV) represents a global health quandary. Among susceptible subjects to this infection those who are on maintenance hemodialysis (HD). The prevalence of HBV infection in HD patients varies markedly from country to country according to the endemicity of the hepatitis viruses [1]. The potential source for hepatitis B virus infection on hemodialysis patients are the practice of multiple blood transfusions making the hospital acquired infections in these patients' earnest complications.

The infection with hepatitis B can lead to cryptogenic liver disease; contribute to acute exacerbation of chronic hepatitis B, or even fulminant hepatitis. Generally, the occurrence of transfusion-transmitted hepatitis B has been steadily reduced over the last years due to the efficacious practice of vaccination [2]; however HBV still remains among mundane virus transmitted by frequent blood transfusions like hepatitis C [3-5].

Screening for blood and blood products is being carried out in national blood banks in Egypt for Hepatitis C virus (HCV) by tenaciousness of categorical immunoglobulin G (IgG) HCV, human immunodeficiency virus (HIV) by IgG and for HBV by hepatitis B virus surface antigen (HBsAg). For HBV the screening method is by resoluteness of concrete antigen S. being the first-line of blood screening for HBV [6]. However, there is growing cognizance that transmission by HBsAg-negative blood may occur during the serologically negative window period, either with positive or negative serological markers for HBV and this situation is referred to as occult HBV infection (OBI) [7,8].

Occult HBV infection was initially described in the tardy 1970 by Tabor et al, 1979 [9] and it is characterized by the presence of HBV DNA in blood or tissues with absence of HBsAg either with or without antibodies to hepatitis B core (anti-HBc) or hepatitis B surface (anti-HBs), outside the pre seroconversion window phase [10, 11].

Perpetual progress in molecular biology techniques has led to more preponderant apperception and diagnosis of OBI. The presence of OBI has been reported in sundry studies among different populations as in patients with chronic liver disorders or hepatocellular carcinoma in integration to salubrious blood donors [12]. Moreover, viral reactivation was tenacious following immunosuppressant situations and even through contingent transmission through transplantation and transfusion [13].

The present study was performed to study the presence of Occult Hepatitis B among Patients under hemodialysis and risk factors associated with this infection

Material and Method

This prospective study was conducted on 96 patients attending Mansoura Univeristy Hospitals. They were 41 males and 55 females with age range from 26 to 65 years. They were complaining of end stage renal disease requiring regular hemodialysis. The study was started from June 2013 to December 2013. We excluded patients with acute or chronic HBV infection (determined by positive HBsAg), patients who were vaccinated against HBV, other causes of liver dysfunction (i.e., primary biliary cirrhosis, autoimmune hepatitis, continued alcohol abuse, autoimmune hepatitis, and HIV infection), and also who were being treated with interferon and/or ribavirin. We obtained complete medical history for each patient, including age, location of residence, HBV vaccination history, blood transfusion history, duration of hemodialysis, etiology of end-stage renal disease. All patients also underwent a complete physical examination. In addition, one hundred sixty seven healthy blood donors were included in the study. The study was approved by Mansoura Faculty of medicine ethical committee and approval written consent was received from each subject participated in the study.

Complete medical history for each patient, including age, residence, previous history of jaundice, HBV vaccination, blood transfusion history, duration of hemodialysis, etiology of end- stage renal disease were obtained. All subjects also underwent a complete physical examination.

Blood samples were obtained from each subject and sera were separated. A serum for each subject was distributed into three aliquots. One for full biochemical tests for liver including alanine aminotransferase (ALT) aspartate aminotransferase (AST), bilirubin and albumin. The other aliquot was used for serological studies by enzyme linked immunosorbant assay for hepatitis C virus IgG (HCV IgG-((Dia-Pro ANTI-HCV, ITALY), hepatitis B surface antigen and anti HBs Ag (HBs Ag and anti HBsAg- BIO-RAD HBsAg, FRANCE), hepatitis B core IgM (HBcIgM- BIO-RAD)) and immunoglobulin G for hepatitis B core (HBcIgG-BIO-RAD)). The third sera aliquots were kept frozen at -70^0 for further molecular study for hepatitis B virus DNA.

Molecular Study of Hepatitis B Virus by PCR

HBV DNA amplification

DNA extraction and Viral load of HBV: Viral DNA was extracted from 200 microns of serum using a QIAamp DNA Blood Mini Kit and a QIAamp viral RNA kit (Qiagen GmbH, Hilden, Germany), following the manufacturer instructions.

Amplification of HBV DNA: HBV DNA detection along with HBV genotyping was performed according to the method described by Naito et al. (2000) [18] based on multiplex PCR using 2 PCR rounds.

The 1st round using universal primers: P1 (sense) and S1-2 (antisense) primers; outer primers (1063 bases) for detection of HBV irrespective of the six genotypes, table 1.

P1	5'-TCA CCA TAT TCT TGG GAA CAA GA-3'(Nucleotide 2823- 2845, universal sense).
S1-2	5'-CGA ACC ACT GAA CAA ATG GC-3' (Nucleotide 685- 704, universal antisense).

Table 1: Sequence of primers P1 and S1-2.

Two second round PCRs were performed for each sample for genotyping of HB. In one reaction, the common universal B2 primer was used as the inner primer (sense) with a combination called mix A for genotypes A, B and C. Mix A consisted of antisense primers BA1R (type A specific), BB1R (type B specific) and BC1R (type C specific).

In the other reaction, primer B2R was used as the inner primer (antisense) with a combination called mix B for genotypes D, E and F. Mix B consisted of sense primers BD1 (type D specific), BE1 (type E specific) and BF1 (type F specific), table 2.

The outer and inner primers targets were within the Pre S1 through S genes.

B2	5'-GGC TCM AGT TCM GGA ACA GT-3' (type A -E, sense, nt 67-86)
BA1 R	5'-CTC GCG GAG ATT GAC GAG ATG T-3' (type A, antisense, nt 113-134)
BB1 R	5'-CAG GTT GGT GAG TGA CTG GAG A-3' (type B, antisense, nt 324-345)
BC1 R	5'-GGT CCT AGG AAT CCT GAT GTT G-3' (type C, antisense, nt165-186)
BD1	5'-GCC AAC AAG GTA GGA GCT-3' (type D, sense, nt2979-2996)
BE1	5'-CAC CAG AAA TCC AGA TTG GGA CCA-3' (type E, sense, nt 2955-2978)
BF1	5'-GYT ACG GTC CAG GGT TAC CA-3' (type F, sense, nt 3032-3051)
B2R	5'GGA GGC GGA TYT GCT GGC AA-3' (type D to F, antisense, nt 3078-3097)

Table 2: Sequence of inner primers involved used in the second round PCR.

Analysis of amplified products

Each sample of HBV genotypes was determined by identifying the genotype specific DNA bands. The two different second round PCR products from one sample were separately electrophoresed in 2 separate lanes. The sizes of PCR products were estimated according to the migration pattern of a 50 bp DNA ladder.

Genotype A	68 bp
Genotype B	281 bp
Genotype C	122 bp
Genotype D	119 bp
Genotype E	167 bp
Genotype F	97 bp

Statistical analysis

Data were analyzed using Sigma Plot software (SPSS, version2). P values were determined using the Chi-square test to study the association between two qualitative variables (compare between proportions); and Student's two-tailed t-test for comparisons between two groups having quantitative variables (ie, compare sample means). Data are presented as percentages, means, and standard deviation (SD). P values less than 0.01 were considered highly significant, and those less than 0.05 were considered significant.

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Results

HBV DNA was detected in 18(18.8%) compared to blood donors (2.4%) with statistically significant difference (P=0.0001). Hepatitis core IgG was positive in 19 patients (19.8%) compared to control group (2.4%). The majority of patients under hemodialysis had positive HBV DNA in absence of any serological markers (72.2%) table 3 and figure 1.

The genotypes of hepatitis B virus in patients under hemodialysis were mainly C (44.4%), followed by A (27.8%) them type B (22.2%), while in healthy control only two genotypes were detected C (50%) and mixed type D&F (50%) with statistically significant difference between patients and control subjects (P=0,0001). Anti HBsAg (HBs Ab) was negative for all subjects, data not shown.

	Dialysis Patients (n = 96)	Blood Donors (n =167)	P
Age Years (mean ±SD)	46.6 ± 12.1	30.1 ± 3.2	P=0.0001
Sex Male (No.-%)	41(42.7%)	99 (59.3%)	P=0.01
ALT (mean± SD)	30.3 ± 14	30.7 ± 15	P=0.61
AST IU/L (mean ± SD)	32.6 ± 17.3	32.6 ± 16.6	P=0.97
Bilirubin mg/dl Mean SD	0.95 ± 0.7	0.92 ± 0.6	P=0.58
Albumin gm/dl Mean± SD	3.5 ± 0.5	3.6 ± 0.5	P=0.394
HCV IgG	41(42%)	31(18.6%)	P=0.0001
HBsAg	0	1(0.6%)	P=0.64
HBcIgM	4(4.2%)	0(0%)	P=0.02
HBVDNA	18(18.8%)	4(2.4%)	P=0.0001
HBcIgG	19 (19.8%)	4 (2.4%)	P=0.07
HBV genotypes A B C D&F	5/18 (27.8%) 4/18(22.2%) 8/18(44.4%) 1/18 (5.6%)	0/4 (0) 0/4(0) 2/4(50%) 2/4(50%)	P=0.0001

Table 3: Demographic and Laboratory finding among patients on hemodialysis and control group.

Figure 1 represents the occult hepatitis B in relation to serological markers HBc IgG and HBc IgM demonstrating that the majority had positive HBV DNA in absence of any serological markers (72.2%).

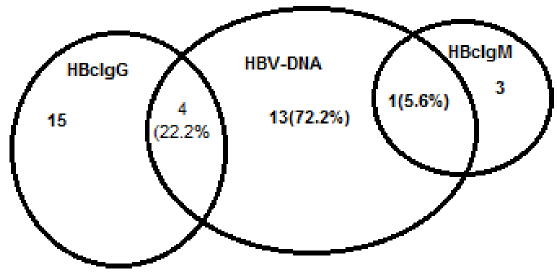

Figure 1: Occult hepatitis B among hemodialysis patients in relation to serological markers HBc IgM and HBc IgG.

The duration of dialysis was significantly longer in patients with occult hepatitis B (46.7± 29.2) compared to those who were negative (21.5±25.9, P=0.0001). Also, increasing number of blood units transfused was significantly higher in patients with occult hepatitis B compared to non-occult hepatitis B patients (P=0.001), table 4.

	Occult hepatitis B Positive (n=18)	Non-Occult Hepatitis (n=78)	P
Age –Years (mean ±SD)	48.7±12.4	46.1±12.1	P=0.9
Sex – N0. (%) Male Female	7(38.9%) 11(61.1%)	34 (43.6%) 44 (56.4%)	P=0.8
ALT IU/L	32.16 ± 17.12	29.8 ± 13.7	P=0.5
AST IU/L	29.7 ± 7.4	33 ± 18.8	P=0.31
Albumin gm/dl	3.7 ± 0.3	3.4 ± 0.56	P=0.4
Bilirubin mg/dl	0.82 ± 0.08	0.97 ± 0.76	P=0.2
Duration Months(mean± SD)	46.7 ± 29.2	21.5 ± 25.9	P=0.0001
Number of Blood units transfusions (mean ±SD)	5.77 ± 4.3	1.8 ± 34	P=0.001
HCV IgG	9(50%)	32(41%)	P=0.8
HBcIgM	1(5.6%)	3 (3.8%)	P=0.7
HBcIgG	4(38.5)	15(16.7%)	P=0.8

Table 4: Demographic and Laboratory finding in Occult hepatitis B and non occult hepatitis B in patients under hemodialysis.

Risk factors analysis for occult hepatitis B in patients under hemodialysis revealed significant association between duration of hemodialysis (P=0, 0001-95%CI 1.01-1.05) and the numbers of transfused blood units (P=.0001 95%CI 1.1-1.5), table 5.

	B	Wald	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
Risk Factor					**Lower**	**Upper**
Number of blood units	0.226	8.411	0.0001	1.254	1.076	1.462
Duration of analysis by months	2.443	28.159	0.000	0.087	1.01	1.05

Table 5: Risk Factors assessment for occult hepatitis B in hemodialysis.

Discussion

End-stage renal disease (ESRD) is a consequential quandary in virtually all countries and the prevalence has incremented considerably in developing countries especially in Middle East countries. Hepatitis viruses transmitted by blood transfusions are another considerable quandary in developing countries.

Egypt was reported to be an endemic area for hepatitis C virus and considered as an intermediate area for hepatitis B virus infection [19]. Both patients undergoing hemodialysis, as well as health care workers in the dialysis unit, are at incremented risk of infection with HBV. HBV can be transmitted in the dialysis units through blood transfusions and environmental surfaces. The epidemiology and clinical paramountcy of occult HBV infection remains controversial with little information about its prevalence in patients on long-term dialysis [20]. Exordium of HBV vaccination, and conventional surveillance for HBV infection has conspicuously reduced its spread, [21,22], however, the quandary persists with many diagnostics challenges.

In this report hepatitis B virus DNA was detected by PCR in 18.8% in patients under hemodialysis. Anterior reports declared the prevalence of occult in Egyptian patients with varying ranges between 5.2% up to 26.8 % on chronic hemodialysis therapy [23].

The prevalence of occult HBV infection in renal dialysis patients ranges between 0% and 58% in published reports in other countries [24-28]. Interpretation is intricate by consequential differences in the composition of the study populations and the caliber of sensitivity of the HBV-DNA assay. These discrepancies in the rate of occult HBV infection in dialysis patients may reflect the diverse prevalence of HBV infection in different countries and within different dialysis units. Other possible explications include sensitivity of molecular biology techniques, size and virological features of the patient groups.

Occult HBV infection can occur in different clinical situations. According to presence or absence of serological markers of HBV there are two conditions. First is the presence of positive HBcIgG with viral DNA at low caliber reflecting perpetual HBV replication. Second situation is the absence of all serological markers for HBV with only viral DNA in serum or- and liver tissue. The main mechanism through which occult infection occurs is not thoroughly understood and several possible mechanisms, such as integration into human DNA and maintenance in peripheral mononuclear cells, subsist [29-32].

Typically, seroclearance of HBsAg is followed by development of anti-HBs with coexisting anti-HBc. If anti-HBs remain negative, anti-HBc accommodates as the only marker betokening past HBV infection as in window phase of infection, decline level of anti-HBs in infection long time ago or in seropositive occult hepatitis B [29].

In the present cohort study HBV DNA was found mainly in seronegative patients (72.2%) while it was associated with HBc IgG in 22.2% and only in one patient(5.6%) with HBc IgM.

Conventionally we could consider patients with positive HBV DNA and core antibodies in instauration state of infection. Anterior studies reported that the majority of HBV-DNA positive individuals had serological evidence of antecedent HBV infection (HBV seropositive), and only 39% were HBV seronegative [25].

The presence of HBV-DNA positive patients with absence of any antibodies conventionally occurs in the presence of mutants that are poorly apperceived by immune system or present in a [33] low-replicative phase of chronicity [34]; and in chronic hepatitis [26,35]. This illustrates the fact that some patients may have had serological markers of HBV infection, but their caliber decline while still perpetuating to have a low grade HBV infection [26]. In patients with end stage renal disease there is customarily hampered immune system that may not respond to infectious agent by engendering antibodies.

The genotypes of hepatitis B virus in patients under hemodialysis were mainly C (44.4%), followed by A (27.8%). B (22.2%), while in healthy control only two genotypes were detected C (50%) and mixed type D&F (50%) with statistically significant difference between patients and control subjects (P=0,0001).

Previous studies in other countries reported different genotypes among hemodialysis patients being genotype D the major genotype present in those patients [36,37]. In Egypt, there are scares reports about the predominant genotypes of hepatitis B, one report described D as the predominant type in patients with hepatitis [38]. The difference between our finding and the others may be contributed to the difference in population size studied, or the different type of patients.

Liver enzymes in patients with occult hepatitis B infection did not show any statistically paramount different from those who were negative for HBV. This finding was withal reported by sundry studies [39,40].

Serum transaminases values incline to be attenuated in dialysis patients and regardless of whether they are dialysis dependent) or not [39,40] and this hampers the apperception of liver damage on the substructure of liver biochemical tests

There was statistically consequential higher prevalence of serological markers for HCV IgG in patients (42%) compared to control (18.6%, P=0.0001), however there was non essential association between the presence of HCV IgG and the presence of OBI.

The prevalence of HCV infection among hemodialysis patients differs in different components of Middle East countries and reported to be 48% in Egypt [41]. Some studies showed associations between HCV and occult HBV infection [28,42] as both viruses are prevalent nosocomial infections that cause higher rates of mortality and morbidity in maintenance hemodialysis patients than in the general population. Other studies found no association between HCV and HBV in hemodialysis patients [43]. Our data showed no significant difference between hepatitis B core antibody levels or occult HBV in patients with and without HCV infection. Theoretically HCV virus

was reported to decrease replication of HBV virus in vitro studies, as HCV core protein is able to inhibit HBV in vitro and serines at positions 99 and 116 are essential for such inhibition [44].

Risk factors analysis for acquiring occult hepatitis B in hemodialysis was performed by multiple logistic regression model. There was statistically consequential association between the duration of dialysis and number of transmitted blood units and presence of occult hepatitis.

Some studies found that time on dialysis were significantly more preponderant in anti-HBc positive than negative HD patients [28]. Other studies found that hemodialysis duration was not significantly different in patients with and without occult HBV infection [45,46].

Another vigorous clue for the association of blood units as a jeopardy factor for acquiring of hepatitis B virus was demonstrated in our study as we detected 4 blood units with hepatitis B virus positive by PCR among salubrious blood donors and more 4 blood donors with positive serological markers for HBc IgG. The chance for acquiring hepatitis B virus from blood units' increase as the transfusion numbers increase.

In Egypt there is a national program for routine analysis for HIV antibodies, hepatitis C virus (HCV) antibodies and HBsAg every three months for all hemodialysis patients with isolation of the HBV positive patients and utilization of dedicated dialysis machines for them.

However, this appears to be insufficient. Application of molecular techniques for detection of hepatitis B viremia in these patients may be required to identify patients with occult hepatitis B with seronegative markers. Therapeutic modalities for those patients should be furthermore implanted especially if associated with hepatitis C virus.

Blood screening by molecular techniques like nucleic acid amplification technology seems a plausible solution to sentinel against the peril of transmission of silent hepatitis B virus.

From this study we can conclude that seronegative occult hepatitis B is mundane among hemodialysis patients. The prolonged duration of dialysis and the number of blood units are major risk factors for acquiring such infection. Modification in laboratory assessment of those patients has to incorporate molecular methods adjacent to serological analysis to discover those patients earlier for therapeutic interference and aversion of infection dissemination.

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